

What is claimed is:

1. A method for identifying compounds that regulate body weight by preferentially regulating peripheral pathways of energy homeostasis, comprising:

a. contacting a putative regulatory compound with a cell which expresses a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R);

b. detecting whether the putative regulatory compound increases said melanocortin receptor activity;

c. contacting said putative regulatory compound with a cell which expresses a melanocortin 4-receptor (MC4-R); and,

d. detecting whether the putative regulatory compound increases MC4-R activity;

wherein putative regulatory compounds that induce greater MC2-R activity or MC5-R activity as compared to MC4-R activity are identified as compounds that regulate body weight by preferentially regulating peripheral pathways of energy homeostasis.

2. The method of Claim 1, wherein said melanocortin receptor of (a) and (b) is MC2-R.

3. The method of Claim 1, wherein said step (b) of detecting is selected from the group consisting of measurement of melanocortin receptor transcription, measurement of melanocortin receptor translation, measurement of phosphorylation of melanocortin receptor, measurement of melanocortin receptor ligand binding activity, measurement of G protein activation, and measurement of melanocortin receptor translocation within a cell.

4. The method of Claim 1, wherein said cell of step (a) is an adipocyte, and wherein said step (b) of detecting is selected from the group consisting of measurement of melanocortin receptor transcription, measurement of melanocortin receptor translation, measurement of phosphorylation of melanocortin receptor, measurement of G protein activation, measurement of melanocortin receptor ligand binding activity, measurement of

melanocortin receptor translocation within a cell, measurement of lipolysis by said cell and measurement of free fatty acid uptake by said cell.

5. The method of Claim 1, wherein said step (d) of detecting is selected from the group consisting of measurement of MC4-R transcription, measurement of MC4-R translation, measurement of phosphorylation of MC4-R, measurement of MC4-R ligand binding activity, and measurement of MC4-R translocation within a cell.

6. A method for identifying compounds that increase body weight by regulating peripheral pathways of energy homeostasis, comprising:

5 a. contacting a cell which expresses a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R) with a POMC compound which binds to and activates said melanocortin receptor in the presence and absence of a putative regulatory compound;

b. detecting whether said putative regulatory compound inhibits said melanocortin receptor activity;

10 wherein putative regulatory compounds that inhibit said melanocortin receptor activity are identified as compounds that increase body weight by regulating peripheral pathways of energy homeostasis.

7. The method of Claim 6, wherein said melanocortin receptor is MC2-R.

8. The method of Claim 6, wherein said POMC compound is a melanocortin compound.

9. The method of Claim 6, wherein said POMC compound is selected from the group consisting of  $\alpha$ -MSH,  $\beta$ -MSH and  $\gamma$ -MSH.

10. A method for identifying compounds that regulate body weight by regulating peripheral pathways of energy homeostasis, comprising:

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- a. contacting a putative regulatory compound with a cell which expresses a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R);
  - b. detecting whether the putative regulatory compound binds to said melanocortin receptor;
  - c. administering compounds which bind to said melanocortin receptor to a non-human test animal and detecting whether the putative regulatory compound regulates the body weight of said test animal;
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wherein putative regulatory compounds that interact with the melanocortin receptor and that regulate the body weight of the test animal are identified as compounds which regulate body weight by regulating peripheral pathways of energy homeostasis.

11. The method of Claim 10, wherein said melanocortin receptor is MC2-R.

12. The method of Claim 10, wherein said test animal is a genetically modified non-human animal comprising a genetic modification within two alleles of its *Pomc* locus, wherein said genetic modification results in an absence of proopiomelanocortin (Pomc) peptide action in said animal.

13 A method for identifying compounds that increase body weight by regulating peripheral pathways of energy homeostasis, comprising:

5 a. contacting a cell which expresses a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R) with a POMC compound which binds to and activates said melanocortin receptor in the presence and absence of a putative regulatory compound;

b. detecting whether said POMC compound binds to said melanocortin receptor;

10 c. administering compounds which bind to said melanocortin receptor to a non-human test animal and detecting whether the putative regulatory compound regulates the body weight of said test animal;

wherein putative regulatory compounds that bind to the melanocortin receptor and that regulate the body weight of the test animal are identified as compounds which increase body weight by regulating peripheral pathways of energy homeostasis.

14. The method of Claim 13, wherein said melanocortin receptor is MC2-R.

15. A method for identifying compounds that regulate body weight by regulating peripheral pathways of energy homeostasis, comprising:

a. contacting a putative regulatory compound with a cell or cell lysate containing a reporter gene operatively associated with a regulatory element of a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R);

b. detecting expression of the reporter gene product;

c. contacting a putative regulatory compound with a cell or cell lysate containing a reporter gene operatively associated with a regulatory element of a melanocortin 4-receptor (MC4-R); and,

d. detecting expression of the reporter gene product;

wherein putative regulatory compounds that increase expression of the reporter gene product of (b) as compared to the reporter gene product of (d) are identified as compounds that regulate body weight by preferentially regulating peripheral pathways of energy homeostasis.

16. The method of Claim 15, wherein said melanocortin receptor is MC2-R.

17. A method for identifying compounds that regulate body weight by regulating peripheral pathways of energy homeostasis, comprising:

a. contacting a putative regulatory compound with a cell or cell lysate containing transcripts of a melanocortin receptor selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R); and,

b. detecting translational inhibition of the melanocortin receptor transcript;

wherein putative regulatory compounds that inhibit said melanocortin receptor transcript are identified as compounds that increase body weight by regulating peripheral pathways of energy homeostasis.

18. The method of Claim 17, wherein said melanocortin receptor is MC2-R.

19. A method for identifying compounds that regulate peripheral pathways of energy homeostasis, comprising:

(a) contacting a putative regulatory compound with an isolated adipocyte; and,

(b) detecting putative regulatory compounds that bind to a melanocortin receptor on said adipocyte, wherein putative regulatory compounds that bind to melanocortin receptors on said adipocytes are identified as compounds that regulate body weight by regulating peripheral pathways of energy homeostasis..

20. The method of Claim 19, wherein said step of detecting further comprises detecting putative regulatory compounds which produce a result selected from the group consisting of stimulation of lipolysis in said adipocytes and inhibition of the uptake of fatty acids by said adipocytes, wherein putative regulatory compounds that bind to melanocortin receptors on said adipocytes and that produce said result are identified as compounds that regulate body weight by regulating peripheral pathways of energy homeostasis.

21. The method of Claim 19, wherein said melanocortin receptor is MC2-R.